REMARKS

Claims 1, 3-5, 7-13, 47, and 49-59 are pending. Claims 7, 8, 10, 11, 47, 50-52, and 55-59 are withdrawn. Claims 2, 6, 14-46, and 48 were previously canceled. Claims 3-4, 13, and 49 are canceled herein without prejudice. Claims 1, 9, 12, and 54 are amended herein to more clearly set forth aspects of the invention. Accordingly, instant claims 1, 5, 9, 12, 53, and 54 are under consideration.

Support for the amendments to the claims is found throughout the specification and in the original claims. Specifically, support for the amendment to claim 1 is presented in original claims 1, 3, and 4 and, for example, in the Abstract and at paragraphs [0008], [0059], [0081], [0086], [0119]- [0121] , and [0124], wherein support for single breast cancer cells and properties thereof and breast cancer cell micrometastases is found and wherein support for a bone marrow microenvironment is found. Support for amendment to claim 9 is found in original claims 3 and 9. Support for amendment to claim 12 is presented in original claims 12 and 13 and, for example, in the Abstract and at paragraphs [0008], [0059], [0081], [0086], [0119]- [0121] , and [0124], wherein support for single breast cancer cells and properties thereof and breast cancer cell micrometastases is found and wherein support for a bone marrow microenvironment is found. Support for amendment to claim 54 is presented in original claims 54, 12 and 4. No issue of new matter is introduced by the amendments to the claims.

Claim Objections

Claim 54 is objected to for depending from claim 50, which has been withdrawn from consideration. Claim 54 is amended herein to depend from claim 12, which is pending. It is, therefore, believed that this objection is obviated and Applicant respectfully requests that the objection be withdrawn.

Rejections under 35 USC § 112

Claims 1, 3, 4, 5, and 9 have been rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. More specifically, claim 1 is viewed as indefinite because the method recites signaling from the microenvironment to "cancer cells", but

also refers to hyperproliferative disorders not involving cancer. It is, therefore, allegedly unclear whether the microenvironment is that of the cancer cells or any cell in which survival signaling is disrupted. Claim 1 is also viewed as indefinite because it is allegedly unclear whether the result of "sensitizing the cells" refers to sensitizing the cells to chemotherapy, biological therapies, radiation therapy, *and* hyperproliferative disorders. Claim 1 also recites "hyperproliferative disorders in a mammal", however, the active steps in the method are viewed as reading on an *in vitro* assay. In light of the above, the metes and bounds are alleged to be unclear.

Claim 1 is amended herein to delete reference to hyperproliferative disorders. Claims 3 and 4 are canceled herein, thereby obviating any rejection of these claims. It is, therefore, believed that the language of the instant claims is definite and thus, reconsideration of this rejection is deferentially requested.

In view of the above, Applicant respectfully requests that the rejection of the claims under U.S.C. § 112, second paragraph, be withdrawn.

Claims 1, 3-5, 9, 12, 13, 49, 53, and 54 have been rejected under 35 USC § 112, first paragraph, for containing subject matter which is allegedly not enabled by the specification. Claims 3-4, 13, and 49 are canceled herein, thereby obviating any rejection of these claims. In view of the amendments to the claims and Applicant's arguments presented herein, the rejection, as it applied to claims 1, 3-5, 9, 12, 13, 49, 53, and 54, is traversed.

The Examiner acknowledges that the specification is enabling for a method for disrupting survival signaling by administering an agent that downregulates alpha 5 beta 1 *in vitro* and a method for blocking the interaction of alpha 5 beta 1 with the extracellular matrix protein fibronectin using a peptide in breast cancer cells *in vitro*. The Examiner maintains that the specification allegedly lacks enabling disclosure for downregulating any integrin or blocking the interaction of any integrin with any extracellular matrix protein or disrupting hyperproliferative disorders other than breast cancer.

Claim 1 is amended herein to be directed to a method for disrupting survival signaling from a bone marrow microenvironment to a single breast cancer cell or breast cancer cell micrometastases, said method comprising administering an agent effective in blocking the interaction of an integrin with an extracellular matrix protein of the bone

marrow microenvironment, wherein the integrin is alpha 5 beta 1 and the extracellular matrix protein is fibronectin, and wherein the method results in sensitizing the single breast cancer cell or breast cancer cell micrometastases to chemotherapy, biological therapies or radiation therapy of primary tumors, cancer metastases or micrometastases in a mammal.

Claim 12 is amended herein to be directed to a method of inhibiting cellular proliferation or inducing cell death or cellular differentiation of a single breast cancer cell or breast cancer cell micrometastases or for treating a single breast cancer cell or breast cancer cell micrometastases in a mammal comprising administering an agent capable of blocking the binding of an integrin to an extracellular matrix protein of the bone marrow microenvironment, wherein the integrin is alpha 5 beta 1 and the extracellular matrix protein is fibronectin, and wherein the method results in inhibiting cellular proliferation or inducing cell death or cellular differentiation of the single breast cancer cell or breast cancer cell micrometastases or in treating the single breast cancer cell or breast cancer cell micrometastases.

The Examiner's comments pertaining to Akamatsu et al (1996, Cancer Res 56:4541-4546) and Schreiner et al. (1991, Cancer Res 51:1738-1740) are hereby acknowledged and issues raised with respect to these references are believed to be addressed herein. Applicant, however, reserves the right to address issues raised in connection with these references at a later date should this be necessitated.

With respect to the Examiner's comments regarding the absence of working examples of *in vivo* results supporting the claimed invention, Applicant offers the following in rebuttal. The experiments described in the specification were conducted *in vitro* to provide a proof of principle that blocking integrin alpha 5 beta 1 interaction with fibronectin disrupts the survival advantage conferred by this signaling pair in cells at **clonogenic density** whose primary interaction is with the substratum in the microenvironment. See also Korah et al. (2004) Cancer Research 64: 4514-4522, which is submitted herewith. The concept can readily be extended to *in vivo* practice by anyone with experience using mouse models of cancer. This assertion is corroborated by numerous articles published in the scientific literature. Indeed, studies have been published wherein small peptide integrin alpha 5 beta 1 antagonists, for example, were

administered to animals either by intraperitoneal injection (Stoeltzing et al. (2003) Int. J. Cancer: 104, 496–503) or intravenous injection (Khalili et al. (2006) Mol Cancer Ther 5:2271–2280). These references are submitted herewith for the Examiner's consideration. One of ordinary skill in the art would certainly be familiar with the techniques described in these papers and would, therefore, be able to replicate the data presented in the instant specification *in vivo* without engaging in undue experimentation. As shown in these studies, injection of a peptide (ATN-161) capable of interfering with integrin alpha 5 beta 1 interaction with fibronectin resulted in inhibition of primary tumor and metastatic growth in animal models. These studies corroborate Applicant's position in this regard because they unequivocally demonstrate that standard techniques are all that is necessary to practice the invention *in vivo*. In light of the above, Applicant asserts that evidence attesting to the applicability of the instant methods to *in vivo* practice exists and one of ordinary skill in the art would appreciate this fact based on the guidance presented in the specification, the level of skill in the art, and the literature available.

Regarding the Examiner's comments pertaining to the Zips et al. reference (2005, In Vivo 19:1-7), Applicant asserts that this paper speaks to the complexity of 3-dimensional solid tumors wherein malignant cell-cell interaction and malignant-nonmalignant cell interactions, vascularization issues, and drug access are cited as significant factors for responsiveness. These factors do not pertain to the situation of a single metastatic malignant cell whose primary interaction is with the structural proteins of the microenvironment, in this case, fibronectin. See also Braun et al. (2000) The New England J. Med. 342:525-533, submitted herewith. As shown in this reference in Figure 1, for example, single metastatic cells and micrometastatic cells have no cell-cell contacts or limited cell-cell contacts because they are at essentially single cell density. In other words, single breast cancer cells and breast cancer cell micrometastases, as presently recited, are at clonogenic density and, as a consequence, their primary interaction is with the substratum in the bone marrow microenvironment. The concept of dormancy is based on these cells lying dormant in these sites for extended periods, benefiting from their interactions with the microenvironment by resisting chemotherapy administered for the very purpose of eliminating these cells. See also Braun et al. (2000) J. Clin. Onc. 18: 80-86, which is submitted herewith. A review article by Wieder (2005, J. Surg. Oncol.

89:207-210), which discusses insurgent micrometastases and properties thereof, is also submitted for the Examiner's consideration.

In light of the above, Applicant respectfully requests that the rejection of the claims under U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 USC § 102

Claims 1, 3-5, 9, 12, 13, 49, 53, and 54 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bates et al. (1995, Cancer Metastasis Review 14:191-203). Claims 3-4, 13, and 49 are canceled herein, thereby obviating any rejection of these claims. In view of the amendments to the claims and Applicant's arguments presented herein, the rejection, as it applied to claims 1, 3-5, 9, 12, 13, 49, 53, and 54, is respectfully traversed.

The claims are amended herein to be directed to a method for disrupting survival signaling from a bone marrow microenvironment to a single breast cancer cell or breast cancer cell micrometastases (claim 1) or a method of inhibiting cellular proliferation or inducing cell death or cellular differentiation of a single breast cancer cell or breast cancer cell micrometastases or for treating a single breast cancer cell or breast cancer cell micrometastases (claim 12), either of said methods comprising administering an agent effective in blocking the interaction of an integrin with an extracellular matrix protein of the bone marrow microenvironment, wherein the integrin is alpha 5 beta 1 and the extracellular matrix protein is fibronectin.

In contrast, Bates et al. do not teach or suggest a method for disrupting survival signaling from a bone marrow microenvironment to a single breast cancer cell or breast cancer cell micrometastases (claim 1) or a method of inhibiting cellular proliferation or inducing cell death or cellular differentiation of a single breast cancer cell or breast cancer cell micrometastases or for treating a single breast cancer cell or breast cancer cell micrometastases (claim 12) as presently claimed. That being the case, the Bates et al. reference fails to teach a recited element of the claims.

It is also noteworthy that Bates et al. view the formation of tumor cell emboli as a requirement for metastasizing tumor cells. See page 200, left column, first full paragraph. Moreover, these authors state that "integrin engagement can protect against or

promote apoptosis" (see page 200, left column, last sentence of first paragraph), which renders it apparent that no uniform rule regarding integrin engagement and cellular response can be applied based on the information available, certainly at the time this review article was published. It also, therefore, follows that this reference suggests that there would be an equal lack of predictability of cellular response with respect to blocking integrin signaling.

In that the Bates et al. reference does not teach at least one recited feature of the instant claims, this document fails to anticipate the claimed invention. This reference also teaches that cellular response to integrin engagement can not be predicted accurately and is influenced by, for example, cell type and degree of cellular aggregation. In view of the above, the rejection, as it applied to claims 1, 3-5, 9, 12, 13, 49, 53, and 54, is respectfully traversed. Reconsideration and withdrawal of the rejection are, therefore, deferentially requested.

Claims 1, 3-5, 9, 12, 13, 49, 53, and 54 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Nista et al. (1997, Int J Cancer 72:133-141). Claims 3-4, 13, and 49 are canceled herein, thereby obviating any rejection of these claims. In view of the amendments to the claims and Applicant's arguments presented herein, the rejection, as it applied to claims 1, 3-5, 9, 12, 13, 49, 53, and 54, is respectfully traversed.

As described above, the instant claims are directed to a method for disrupting survival signaling from a bone marrow microenvironment to a single breast cancer cell or breast cancer cell micrometastases (claim 1) or a method of inhibiting cellular proliferation or inducing cell death or cellular differentiation of a single breast cancer cell or breast cancer cell micrometastases or for treating a single breast cancer cell or breast cancer cell micrometastases (claim 12), said methods comprising administering an agent effective in blocking the interaction of an integrin with an extracellular matrix protein of the bone marrow microenvironment, wherein the integrin is alpha 5 beta 1 and the extracellular matrix protein is fibronectin.

Nista et al. do not teach or suggest a method for disrupting survival signaling from a bone marrow microenvironment to a single breast cancer cell or breast cancer cell micrometastases (claim 1) or a method of inhibiting cellular proliferation or inducing cell death or cellular differentiation of a single breast cancer cell or breast cancer cell

micrometastases or for treating a single breast cancer cell or breast cancer cell micrometastases (claim 12) as presently claimed. That being the case, this reference fails to teach a recited element of the claims. Moreover, all of the results and discussion thereof presented in the Nista et al. reference relate to cell populations that are at a proliferative density, wherein cell-cell contact occurs and contributes to cellular response. In other words, the cell populations examined were not plated at clonogenic density, but rather were plated at much higher densities. In light of that which was understood in the field at the publication date of this reference, one of ordinary skill in the art would have appreciated that the response of single breast cancer cells or breast cancer micrometastases could not be predicted based on assays performed on cells plated at proliferative densities. In view of the above, this reference at the very least fails to teach a recited element of the claims.

Moreover, it is apparent that the postulated contribution of alpha 5 beta 1 integrin-fibronectin interaction to adriamycin-resistant MCF-7 cell survival can not be extrapolated to all breast cancer cells. This is evidenced by the fact that the adriamycin-sensitive MCF-7 (WT) cells are quite distinct with respect to cellular response to the experimental conditions assayed. The references authored by Akamatsu et al. and Schreiner et al. cited by the Examiner on the PTO-892 form also attest to the lack of predictability when attempting to extrapolate cellular response to integrin engagement from one cell type to another or under different culturing conditions. Knowing this, one of ordinary skill in the art would not be convinced that the Nista et al. reference is relevant to the instant claims.

In view of the amendments to the claims and arguments presented herein, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §102 and withdraw the rejection.

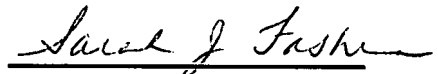
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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September 18, 2007

Enclosures: Petition for a One Month Extension of Time
Information Disclosure Statement